Remarks and Arguments

Claims 1-19 have been presented for examination. Claims 1, 4-8, 11, 13-16 and 18-19 have been amended. Claims 2, 3, 9 and 10 have been canceled.

Claims 1-19 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, claims 1-19 have been indicated as unclear because the preamble of claim 1 recited "measuring" the binding of analyte molecules whereas the last step recited in claim 1 recited "detecting" the binding of analyte molecules. The examiner indicates that it is unclear how the measuring and detecting steps are related. In response, claim 1 has been amended to recite in the preamble, "measuring the binding of analyte molecules" whereas new step (f) recites "measuring an electrical property generated by the galvanic element in the electronic circuits of the circuit surface, thereby enabling the binding of the analyte molecules to the probe molecules to be measured." Accordingly, the preamble and step (f) now agree in terminology and claim 1 is believed to be clear in this respect.

Original step (c) of claim 1 was considered indefinite because it recited that the analyte molecules, "together with the electrically conductive nanoparticles", were bound to the probe molecules. The examiner indicated that it was unclear whether the nanoparticles participated in the binding or interacted directly with the probe molecules. In response, claim 1 has been amended to recite: "...(c) binding nanoparticles having a metal surface to the analyte molecules, (d) placing the analyte molecules in the vicinity of the probe molecules in order to facilitate binding of the analyte molecules to the probe molecules..." It is believed the relationship between the analyte molecules and the nanoparticles is now clear.

Claim 1 was also rejected because it originally recited the phrase "making the circuits of the circuit surface electrically reading the presence of the nanoparticles" which the examiner considered unclear. In response, claim 1 has been amended to eliminate this phrase and to recite instead in steps (e) and (f) creating "a galvanic element including the contact spot and the counterelectrode, and (f) measuring an electrical property generated by the galvanic element in the electronic circuits of the circuit surface." New steps (e) and (f) are believed to be clear.

Claim 2 has been canceled, thereby rendering the rejection of this claim moot.

Claims 3, 9 and 13-17 have been rejected for lack of antecedent basis for the term "the circuit" in claim 3. As claims 3 and 9 have been canceled, this rejection is moot with respect to them. The term "the circuit" does not appear in claims 13-17, which were presumably rejected for their dependence on claim 9.

Claims 3 and 9-17 have been rejected for reciting the unclear phrase "reading a voltage on the nanoparticles" originally recited in claim 3. As claims 3 and 9 have been canceled, this rejection is moot with respect to them. The phrase "reading a voltage on the nanoparticles" does not appear in claims 11-17, which were presumably rejected for their dependence on claim 3.

Claim 7 has been rejected because the phrase "the nanoparticles are already bound to the analyte molecules is indefinite because the parent claim recites several steps and it is unclear to which step the phrase refers. In response, claim 7 has been amended to recite "…the nanoparticles are bound to the analyte molecules before step (d)…" making it clear to which step the claim refers. Claim 7 is therefore believed to be clear and concise as required by 35 U.S.C. §112, second paragraph.

Claims 9 and 13-17 have been rejected for lack of antecedent basis for the term "the countersurface" originally recited in claim 9. As claim 9 has been canceled, this rejection is moot with respect to it. The term "the countersurface" does not appear in claims 13-17, which were presumably rejected for their dependence on claim 9.

Claims 9 and 13-17 have been rejected for reciting the phrase "measured via the nanoparticles" which the examiner considered as unclear whether the nanoparticles themselves participated in the measuring process. This phrase was originally recited in claim 9. As claim 9 has been canceled, this rejection is moot with respect to it. The phrase "measured via the nanoparticles" does not appear in claims 13-17, which were presumably rejected for their dependence on claim 9.

Claims 10-12 have been rejected for lack of antecedent basis for the term "the metal surface" originally recited in claim 10. As claim 10 has been canceled, this rejection is moot with respect to it. However, the limitations of claim 10 have now been included in amended claim 1. Amended claim 1 recites, in lines 15-16, "…introducing an electrolyte adjacent the circuit surface and establishing an electrical contact between the metal surfaces on the nanoparticles…" The term "the metal surface" finds

antecedent basis in claim 1, line 7. The term "the metal surface" does not appear in claims 11-12, which were presumably rejected for their dependence on claim 10.

Claim 15 was rejected because it recites limitations that indicate that contact between the nanoparticles and the contact spot is made by an external magnetic field, but this claim was dependent on claim 9 which indicated that contact between the nanoparticles and the contact spot is made by movement of a countersurface. Claim 15 has now been amended to make it dependent on claim 13 which recites that the contact between the nanoparticles and the contact spot is established by the nanoparticles touching the contact spot. Amended claim 15 now recites that the "touching" is accomplished by the magnetic field and is believed to be clear.

Claims 18 and 19 have been rejected for the recitation of the phrase "amplified in a previous step" because it is unclear to which step this phrase refers. In response, claim 18, which is dependent on claim 1, has bee amended to recite "…the analyte molecules are amplified prior to step (d)…" and, thus, clearly refers to step (d) of claim 1.

Claims 18 and 19 have also been rejected for lack of antecedent basis for the phrase "…the biotin groups of the analyte molecules…" This phrase has been amended to "…enabling binding of the nanoparticles to biotin groups of the analyte molecules…" thereby eliminating the improper reference. Claim 19 does not recite the phrase "…the biotin groups of the analyte molecules…" and was presumably rejected for its dependence on claim 18.

Claims 18 and 19 were further rejected for reciting the phrase "…being coated with streptavidin…" which the examiner found unclear as to how being coated with streptavidin binds the nanoparticles to the analyte molecules. Claim 18 has been amended to recite "…the analyte molecules are amplified … using a biotinylated primer, and the nanoparticles are coated with streptavidin, enabling binding of the nanoparticles to biotin groups of the analyte molecules by a biotin-streptavidin binding pair." It is believed that this rewording clearly indicates the binding mechanism.

Claim 19 was also rejected for lack of antecedent basis for the phrase "the biotin-streptavidin pair." Claim 18 has been amended, in line 6, to recite "a biotin-streptavidin pair" to provide an antecedent basis for the recitation in claim 19. Claim 19 has also

been rejected for reciting that another binding pair is substituted for the biotin-streptavidin pair, but claim 18, on which claim 19 depends, recites the use of a biotinylated primer and streptavidin coated nanoparticles and, thus, would seem to require a biotin-streptavidin pair. In response, claim 19 has been amended to recite "wherein the analyte molecules are amplified prior to step (d) by polymerase chain reactions (PCR) using a primer, and the nanoparticles are coated with a substance that binds to molecules in the primer, enabling binding of the nanoparticles to the analyte molecules so that instead of the biotin-streptavidin binding pair another binding pair is used." Thus, as amended, claim 19 no longer requires the use of a biotinylated primer and streptavidin coated nanoparticles and is now believed to be clear.

Claims 1-4, 6-8, 10, 11, 18 and 19 have been rejected under 35 U.S.C. §103(a) as obvious over PCT Patent Publication No. WO 99/27367 (Knoll) in view of U.S. Patent No. 6,391,558 (Henkens.) The examiner comments that the Knoll reference discloses all of the claimed limitations with the exception that it does not explicitly disclose the PCR amplification recited in claims 18 and 19. However, the examiner claims that the Henkens reference discloses PCR techniques in conjunction with detection of nucleic acids using electrodes with immobilized probes. The examiner concludes that it would have been obvious to combine the teachings of Knoll and Henkens based on the teaching of Henkens that covalent attachment of the probe molecules is a preferred mode.

In accordance with one embodiment of the invention described in paragraphs [18] and [44] to [46] a galvanic element is constructed by binding nanoparticles with a metal surface to probe molecules, adding an electrolyte, and contacting the nanoparticles with a contact spot. This galvanic element generates a voltage or a current, which can be detected with the electronic circuits on the circuit surface.

The examiner correctly states that "Knoll teaches the detection of analytes using potentiometric measurement methods (co1.18 ln.30 - co1.20 ln.5) where contact of an electroconductive marker to a potentiometric electrode allows ions to flow through an aqueous measuring medium (which is thus an electrolyte) to generate an electric current." However, as can be seen in Figure 31 of the Knoll reference, the nanoparticles may influence the potential of an electrode or an ion current through a

membrane, but the nanoparticles 1) are electrically isolated and 2) do not form one of the electrodes of a galvanic element. In the present invention, the nanoparticles (or the metal surface of the nanoparticles respectively) form one of the electrodes of a galvanic element by enabling an electrical contact between the nanoparticles and the contact spot on the circuit surface.

The Henkens reference, as suggested by the examiner, teaches methods for the detection of nucleic acids using electrodes with immobilized probe molecules and analyte molecules bound to reporter particles. However, the Henkens disclosure measures the presence and quantity of the reported particles by a technique that the Henkens disclosure refers to as "pulse amperometry" or "differential pulse amperometry", a technique in which current pulses are applied to a working electrode on which the probe molecules have been immobilized and to a reference electrode. The responses of each electrode are monitored to determine the quantity of reporter particles present. Henkens does not disclose the formation of a galvanic element that, in turn, generates an output that can be measured. Thus, neither of the cited references discloses the construction of a galvanic element.

Claim 1 has been amended by incorporating the limitations of original claim 10. Accordingly, original claim 10 has now been canceled. As amended, claim 1 recites, in steps (e) and (f), "... (e) introducing an electrolyte adjacent the circuit surface and establishing an electrical contact between the metal surface on the nanoparticles and the contact spot to create a galvanic element including the contact spot and the counterelectrode, and (f) measuring an electrical property generated by the galvanic element in the electronic circuits of the circuit surface..." As discussed above, neither the Knoll reference nor the Henkens reference discloses such an arrangement. Consequently, the combination cannot disclose such an arrangement. The examiner points to Knoll, column 18, line 30 to column 20, line 5, as disclosing the claimed arrangement. However, at this point, the Knoll disclosure refers to potentiometric detection in which a current is applied across a film having the probe molecules immobilized thereon and the voltage is measured to detect the presence and quantity of the analyte molecules. Knoll does not disclosure the construction of a galvanic element

as claimed in amended claim 1. Consequently, amended claim 1 patentably distinguishes over the cited reference combination.

Claims 2-4, 6-8, 10, 11, 18 and 19 depend, either directly or indirectly on amended claim 1, and incorporate the limitations thereof. Therefore, these latter claims also patentably distinguish over the cited reference combination in the same manner as amended claim 1.

Claims 5 and 12 have been rejected under 35 U.S.C. §103(a) as obvious over Knoll in view of Henkens and further in view of U.S. Patent No. 6,207,369 (Wohlstadter.) The examiner comments that Knoll and Henkens disclose the recited limitations with the exception that they do not disclose the use of polyene molecules to conduct an electrical signals as recited in claim 12 (claim 5 has been canceled, thereby rendering its rejection moot.) The examiner indicates that Wohlstadter discloses the use of a linking chain in the polyene class to insure low resistance transfer of electrons from an electrode. The examiner concludes that it would have been obvious to combine the teachings of Knoll, Henkens and Wohlstadter because Wohlstadter teaches the use of polyacetylene for the use set forth in the claim.

As discussed above, the combination of Knoll and Henkens does not teach the formation of a galvanic element as claimed. Adding Wohlstadter to this combination does not change this conclusion because Wohlstadter detects the presence and quantity of the analyte molecules by eletrochemiluminescence, not by forming a galvanic element and then measuring the electrical properties of that element as recited. Since claim 12 is dependent on amended claim 1 and incorporates the limitations thereof, it distinguishes over the cited reference combination in the same manner as claim 1.

Claims 9, 13, 16 and 17 have been rejected under 35 U.S.C. §103(a) as obvious over Knoll in view of Henkens and further in view of PCT Patent Publication No. WO 02/054052 A1 (Fish.) The examiner comments that Knoll and Henkens disclose the recited limitations with the exception that they do not disclose moving a countersurface to press nanoparticles against a contact spot. The examiner indicates that Fish discloses the detection of analyte molecules with an electrode-based scheme in which an opposing surface with an electrode is moved to make contact with an electrically-

readable particle. The examiner concludes that it would have been obvious to combine the teachings of Knoll, Henkens and Fish because Fish teaches the use of the movable surface allows the electrochemistry to be performed quickly and at low cost.

The Fish reference discloses analyte detection by binding the analyte molecules to electrically-readable particles and then detecting the presence and quantity of the particles by placing the particles with the bound analyte molecules in an electric cell with a movable wall. As the wall is moved, the electrical properties of the cell are measured. These electrical properties are stated to include current, resistance, capacitance, inductance, voltage, magnetic flux or phase shift.

As discussed above, the combination of Knoll and Henkens does not teach the formation of a galvanic element as claimed. Adding Fish to this combination does not change this conclusion because Fish detects the presence and quantity of the analyte molecules by measuring electrical changes in a measuring cell, not by forming a galvanic element and then measuring the electrical properties of that element as recited. Since claims 13, 16 and 17 are dependent on amended claim 1 and incorporate the limitations thereof, they distinguish over the cited reference combination in the same manner as claim 1.

Claim 14 has been rejected under 35 U.S.C. §103(a) as obvious over Knoll in view of Henkens and in view of Fish and further in view of Wohlstadter. The examiner comments that Knoll, Henkens and Fish disclose the recited limitations with the exception that they do not disclose that the analyte is collected on a surface opposite to the surface on which the detecting electrode is mounted. The examiner indicates that Wohlstadter discloses several electrode-based detection configurations in which an analyte is collected on a surface opposite to the surface on which the detecting electrode is mounted. The examiner concludes that it would have been obvious to combine the teachings of Knoll, Henkens, Fish and Wohlstadter because Wohlstadter teaches the use of a configuration that allows the electrode to be protected from contamination.

The combination of Knoll, Henkens and Fish has been discussed above and does not teach the formation of a galvanic element as claimed. Adding Wohlstadter to this combination does not change this conclusion because, also as discussed above,

Wohlstadter detects the presence and quantity of the analyte molecules by electrochemiluminescence, not by forming a galvanic element and then measuring the electrical properties of that element as recited. Since claim 14 is dependent on amended claim 1 and incorporates the limitations thereof, it distinguishes over the cited reference combination in the same manner as claim 1.

Claim 15 has been rejected under 35 U.S.C. §103(a) as obvious over Knoll in view of Henkens in view of Fish in view of Wohlstadter and further in view of an article entitled "Metal Nanoparticle-Based Electrochemical Stripping Potentiometric Detection of DNA Hybridization" (Wang.) The examiner comments that Knoll, Henkens and Fish disclose the recited limitations with the exception that they do not disclose that that an analyte molecule/particle complex is first bound to a surface via a probe molecule and then later the bond is broken and the freed complex detected. The examiner comments that the Wang reference discloses binding gold nanoparticles to a target oligonucleotide and then later separating the gold nanoparticle and detecting it at an electrode. The examiner concludes that it would have been obvious to combine the teachings of Knoll, Henkens, Fish and Wang because Wang teaches that the dissolution step increases sensitivity of the detection apparatus.

As discussed above, the combination of Knoll, Henkens and Fish does not teach the formation of a galvanic element as claimed. Adding Wang to this combination does not change this conclusion because Wang detects the presence and quantity of the analyte molecules by stripping gold nanoparticles from their bound relationship with the analyte molecules by electrochemical reactions at a working electrode and then measuring electrical changes at the working electrode by potentiometric means, not by forming a galvanic element and then measuring the electrical properties of that element as recited. Since claim 15 is dependent on amended claim 1 and incorporates the limitations thereof, it distinguishes over the cited reference combination in the same manner as claim 1.

In light of the forgoing amendments and remarks, this application is now believed in condition for allowance and a notice of allowance is earnestly solicited. If the examiner has any further questions regarding this amendment, he is invited to call applicants' attorney at the number listed below. The examiner is hereby authorized to

charge any fees or direct any payment under 37 C.F.R. §§1.17, 1.16 to Deposit Account number 50-3969.

Respectfully submitted

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